

CYTOLOGIC SCREENING FOR ESOPHAGEAL CANCER: RESULTS FROM 12,877 SUBJECTS FROM A HIGH-RISK POPULATION IN CHINA

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Linxian, China, has one of the highest esophageal-cancer mortality rates in the world. In 1983, esophageal balloon-cytology screening was performed to identify subjects eligible for 2 nutrition-intervention trials in Linxian; 12,877 subjects had cytology slides which were satisfactory for diagnosis. Of the 12,649 subjects with squamous-cell diagnoses, 31% were normal by Chinese cytologic criteria; 38% showed hyperplasia; 21% showed dysplasia 1; 6% showed dysplasia 2; 2% showed near-cancer; and 2% showed cancer. Of the 1,471 subjects with columnar-cell diagnoses, 31% were normal; 44% showed hyperplasia; 16% showed dysplasia 1; 4% showed dysplasia 2; 2% showed near-cancer; and 3% showed cancer. Squamous dysplasia and cancer were more common among females than males, while columnar dysplasia and cancer showed male predominance. The prevalence of dysplasia and cancer of both cell types increased with age. The prevalence of squamous dysplasia was significantly higher than in earlier balloon-cytology screenings in Linxian, probably reflecting changes in cytologic classification.

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The Taihang mountain region of North China has one of the highest rates of esophageal cancer in the world. In Linxian, Henan Province, the age-adjusted mortality rates in 1973–1975 were 161 per 100,000 for men and 103 per 100,000 for women, and by age 75 the cumulative mortality from esophageal cancer was over 20% for both sexes (Li *et al.*, 1980; Li, 1982).

Over the past 40 years, Chinese scientists have performed many cytologic studies aimed at identifying harmful exposures which might be lessened or removed. These studies have led to several etiologic hypotheses, including multiple nutrient deficiencies, consumption of pickled vegetables and moldy foods, ingestion of high levels of exogenous nitrosamines, increased production of endogenous nitrosamines, physical trauma to the esophageal mucosa, and others (Li, M.X., *et al.*, 1980; Yang, 1980; Li, J.Y., *et al.*, 1989). In addition to these etiologic studies, Chinese scientists have developed esophageal balloon cytology (lǎ wǎng) screening as an early detection technique to identify surgically curable pre-cancerous and early cancerous esophageal lesions (Shen and Shu, 1982; Shu, 1983; Shen, 1984).

The presence of prominent nutrient deficiencies in a population at very high risk for esophageal cancer suggested the usefulness of conducting an intervention study to test the hypothesis that nutritional supplementation could affect esophageal-cancer experience. The ability of balloon cytology to screen for individuals with pre-cancerous esophageal lesions suggested the possibility of selecting an especially high-risk group from this population for separate study (Blot and Li, 1985). In this setting, the US National Cancer Institute and the Cancer Institute of the Chinese Academy of Medical Sciences decided to collaborate in the conduct of 2 nutrition-intervention trials in Linxian, a dysplasia trial limited to subjects with cytologically demonstrated esophageal dysplasia, and a general population trial drawing from all subjects in a specified age range in targeted communes (Blot and Li, 1985; Li *et al.*, 1986).

Before such intervention studies could begin, baseline balloon cytology screening was needed to identify and exclude subjects with prevalent esophageal cancer and to identify subjects appropriate for inclusion in the dysplasia trial. We now report the methods and results of that baseline screening.

MATERIAL AND METHODS

Balloon cytology screening

In November and December, 1983, scientists from the Cancer Institute of the Chinese Academy of Medical Sciences (CICAMS) in Beijing and from Henan Medical University (HMU) in Zhengzhou conducted a population-based esophageal balloon cytology screening in Yaocun, Rencun, and Donggang communes in Linxian, Henan Province. All inhabitants of these 3 communes between the ages of 40 and 69 were invited to participate, without regard for symptoms, family history or other factors. Teams of cytologists and other medical workers went from village to village and performed the balloon-swallowing examinations, using standard collection methods (Shu, 1983). The smears were stained with Papanicolaou stain and read under the direction of Dr. Qiong Shen of HMU and Dr. Shu-Fan Liu of CICAMS, who personally reviewed all diagnoses of dysplasia, near-cancer or cancer. Data recorded for each subject included name, gender, age, birth date, an identification number, and the cytology diagnosis.

Cytologic categories

There were 6 cytologic categories for squamous cells and 6 cytologic categories for columnar cells used in the 1983 screening. The category names and the defining nuclear criteria were the same for both cell types; the identification of squamous- or columnar-cell type was based on cytoplasmic characteristics. The cytologic categories and criteria, listed in order of presumed increasing severity, were as follows:

Normal (zhèng cháng): most cells are normal intermediate cells, with 10 to 15% normal superficial cells. Rare parabasal cells may be present. Hyperplasia (qīng dù zēng shēng): the nuclei are mildly hyperchromatic and enlarged, being 2 or more but less than 3 times the size of nuclei in normal intermediate cells. Dysplasia 1 (zhòng dù zēng shēng yī jí): the nuclei are hyperchromatic, with finely granular and evenly distributed chromatin. The nuclei are 3 or more but less than 4 times the size of the nuclei of normal intermediate cells. When hyperplasia cells are present in the smear, finding a single cell meeting the criteria for dysplasia 1 is sufficient for this diagnosis. Dysplasia 2 (zhòng dù zēng shēng èr jí): the pattern is similar to dysplasia 1 except that the abnormal nuclei are 4 or more but less than 5 times the size of the nuclei of normal intermediate cells. When hyperplasia or dysplasia 1 cells are

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present in the smear, finding a single dysplasia 2 cell is sufficient for this diagnosis. Near-cancer (jīn ái): the pattern is similar to dysplasia 2, except that the abnormal nuclei are 5 or more times the size of the nuclei of normal intermediate cells. Finding a single near-cancer cell is sufficient for this diagnosis. Typical cancer cells are absent. Cancer (ái; lín ái; xiàn ái): typical cancer cells are present. Typical cancer cells have coarse chromatin granules which vary in size and are irregularly distributed. They may have irregularly thickened and irregularly contoured nuclear membranes. The nuclear-cytoplasmic (N/C) ratio is increased. Nucleoli may be present (nucleoli are seen only occasionally in squamous-cell cancer; they are always seen in adenocarcinoma).

Additional descriptions and illustrations of Chinese esophageal cytologic categories can be found in previous publications (Shen and Shu, 1982; Shu, 1983, 1985).

Analysis

In 1983, the 40- to 69-year-old target population of the 3 screened communes was 34,779. Of these, 12,978 (37.3%) underwent a balloon examination. In addition, 571 individuals less than 40 years old and 43 individuals over 69 years old were examined. Of the total 13,051 persons screened in 1983, 174 (1.3%) had slides which were unsatisfactory for diagnosis. Our analysis was performed on the remaining 12,877 subjects.

Overall differences in the distribution of cytology results by gender and by age groups were evaluated using the chi-square test; age and cytology diagnoses were correlated as Spearman correlations, using SAS (SAS Institute, 1985).

RESULTS

Table I shows the gender, age, and commune distribution of the 12,877 subjects with cytology diagnoses. There were approximately equal numbers of men and women screened; 95.3% of the subjects were in the 40- to 69-year-old target population. The mean ages of males and females were 52.2 years and 51.2 years respectively. The mean ages by commune were: Yaocun 51.2 years, Rencun 51.4 years and Donggang 52.2 years.

Of the 12,877 subjects, 11,406 (88.6%) had only a squamous-cell diagnosis, 228 (1.8%) had only a columnar-cell diagnosis, and 1,243 (9.7%) had both squamous- and columnar-cell diagnoses. In subjects with both squamous-cell and columnar-cell diagnoses, the squamous-cell diagnosis was more severe in 254 (20.4%), while the columnar-cell diagnosis was more severe in 121 (9.7%); the 2 diagnoses were of equal severity in 868 (69.8%). There were no subjects with both squamous-cell and glandular cancers.

TABLE I - GENERAL CHARACTERISTICS OF PARTICIPANTS IN THE 1983 BALLOON CYTOLOGY SCREENING

Variable	Number	Percent
Gender		
Male	6408	49.8
Female	6469	50.2
Age group		
20-9	29	0.2
30-9	538	4.2
40-9	4603	35.7
50-9	5236	40.7
60-9	2431	18.9
70+	40	0.3
Commune		
Yaocun	3587	27.9
Rencun	4324	33.6
Donggang	4966	38.6
Total	12,877	

Tables II and III show the cytology results of the 12,649 subjects who had squamous-cell diagnoses and the 1,471 subjects who had columnar-cell diagnoses, stratified by gender. Among the squamous-cell results (Table II), the diagnoses normal and hyperplasia were slightly more common among males than among females, and each of the diagnoses dysplasia 1, dysplasia 2, near-cancer and cancer were more common among females than among males. The combined prevalence of squamous dysplasia and cancer was higher in females than in males (34% vs. 28%, $p < 0.005$). In the columnar results (Table III), the opposite tendency was evident, with normal diagnoses being more common in females and all other diagnoses being more common in males.

Tables IV and V show the squamous-cell and columnar-cell diagnoses stratified by age groups, and the mean age of each diagnosis. Increasing age was positively correlated with worse cytologic diagnosis for both squamous-cell ($r = 0.16$, $p < 0.001$) and columnar-cell ($r = 0.21$, $p < 0.001$) diagnoses. In addition, both for squamous-cell and for columnar-cell types, the mean ages increased steadily with increasing severity of diagnosis. The difference in mean age between normal and cancer was 5.4 years for the squamous-cell diagnoses and 7.0 years for the columnar-cell diagnoses.

DISCUSSION

The esophageal balloon cytology screening reported here was the baseline cytologic examination for the Linxian nutrition intervention trials (Blot and Li, 1985; Li *et al.*, 1986). The purposes of the screening were to identify prevalent cancer cases, so they could be treated and excluded from the trials, and to identify subjects with cytologic evidence of esophageal dysplasia, so they could be invited to participate in the dysplasia trial.

The target population for this screening was all inhabitants, between 40 and 69 years of age, of 3 communes in northern Linxian. Thirty-seven percent of this target population underwent a balloon examination and 98.7% of those examined had cytology smears which were satisfactory for diagnosis. The

TABLE II - SQUAMOUS-CELL RESULTS OF THE 1983 BALLOON CYTOLOGY SCREENING EXAMINATIONS, BY GENDER

Squamous cytology result	Gender		
	Male	Female	All
Normal	2046 (32.5%)	1880 (29.6%)	3926 (31.0%)
Hyperplasia	2511 (39.9%)	2321 (36.5%)	4832 (38.2%)
Dysplasia 1	1196 (19.0%)	1411 (22.2%)	2607 (20.6%)
Dysplasia 2	316 (5.0%)	476 (7.5%)	792 (6.3%)
Near-cancer	98 (1.6%)	130 (2.0%)	228 (1.8%)
Cancer	122 (1.9%)	142 (2.2%)	264 (2.1%)
Total	6289 (100%)	6360 (100%)	12,649 (100%)

Chi-square (5df) = 70.15; $p < 0.01$.

TABLE III - COLUMNAR-CELL RESULTS OF THE 1983 BALLOON CYTOLOGY SCREENING EXAMINATIONS, BY GENDER

Columnar cytology result	Gender		
	Male	Female	All
Normal	179 (25.6%)	277 (35.9%)	456 (31.0%)
Hyperplasia	315 (45.0%)	338 (43.8%)	653 (44.4%)
Dysplasia 1	131 (18.7%)	101 (13.1%)	232 (15.8%)
Dysplasia 2	33 (4.7%)	25 (3.2%)	58 (3.9%)
Near-cancer	16 (2.3%)	11 (1.4%)	27 (1.8%)
Cancer	26 (3.7%)	19 (2.5%)	45 (3.1%)
Total	700 (100%)	771 (100%)	1471 (100%)

Chi-square (5df) = 25.50; $p < 0.001$.

TABLE IV - SQUAMOUS-CELL RESULTS OF THE 1983 BALLOON CYTOLOGY SCREENING, BY AGE GROUPS

Squamous cytology result	Age group					Average age (yrs)
	< 40 yrs	40-49 yrs	50-59 yrs	60+ yrs	All	
Normal	239 (43.1%)	1659 (36.7%)	1455 (28.4%)	573 (23.5%)	3926 (31.0%)	50.1
Hyperplasia	215 (38.7%)	1723 (38.1%)	1972 (38.5%)	922 (37.8%)	4832 (38.2%)	51.6
Dysplasia 1	77 (13.9%)	808 (17.9%)	1111 (21.7%)	611 (25.1%)	2607 (20.6%)	52.9
Dysplasia 2	17 (3.1%)	229 (5.1%)	364 (7.1%)	182 (7.5%)	792 (6.3%)	53.3
Near-cancer	1 (0.2%)	64 (1.4%)	98 (1.9%)	65 (2.7%)	228 (1.8%)	54.4
Cancer	6 (1.1%)	44 (1.0%)	128 (2.5%)	86 (3.5%)	264 (2.1%)	55.5
Total	555 (100%)	4527 (100%)	5128 (100%)	2439 (100%)	12649 (100%)	51.7

Chi-square (15df) = 294.68; $p < 0.001$.

TABLE V - COLUMNAR-CELL RESULTS OF THE 1983 BALLOON CYTOLOGY SCREENING, BY AGE GROUPS

Columnar cytology result	Age group					Average age (yrs)
	< 40 yrs	40-49 yrs	50-59 yrs	60+ yrs	All	
Normal	31 (44.9%)	202 (37.0%)	171 (27.8%)	52 (21.7%)	456 (31.0%)	49.6
Hyperplasia	30 (43.5%)	249 (45.6%)	269 (43.7%)	105 (43.8%)	653 (44.4%)	51.0
Dysplasia 1	7 (1.5%)	70 (12.8%)	109 (17.7%)	46 (19.2%)	232 (15.8%)	52.9
Dysplasia 2	1 (1.5%)	9 (1.7%)	33 (5.4%)	15 (6.3%)	58 (3.9%)	54.7
Near-cancer	0 (0.0%)	9 (1.7%)	9 (1.5%)	9 (3.8%)	27 (1.8%)	54.5
Cancer	0 (0.0%)	7 (1.3%)	25 (4.1%)	13 (5.4%)	45 (3.1%)	56.6
Total	69 (100%)	546 (100%)	616 (100%)	240 (100%)	1471 (100%)	51.7

Chi-square (15df) = 62.86; $p < 0.001$.

gender and age distributions of the screened population were similar to those of the total 40- to 69-year-old population of the 3 communes (data not shown).

When stratified by gender, the results of the screening showed that squamous dysplasia and cancer were more common in females than in males, and that glandular dysplasia and cancer were more common in males than in females. Taking the cell types together, there was a slight female predominance of dysplasia and cancer. Since the reported incidence and mortality rates for esophageal cancer in Linxian are consistently higher for males than for females (M:F = 3:2) (Li *et al.*, 1980; Zhang *et al.*, 1990), the slight female predominance of dysplasia and cancer in this screening was unexpected and remains unexplained. Anecdotal accounts that women in Linxian are less likely than men to see a doctor when they are ill raise the possibility that esophageal cancer may be under-diagnosed clinically in women in this population.

When stratified by age, the results of the screening showed a positive correlation between age and the severity of cytologic diagnosis, and the mean ages of subjects grouped by their cytologic diagnoses increased steadily with the severity of those diagnoses. These findings are consistent with the increasing incidence and mortality of esophageal cancer with age in this population (Li *et al.*, 1980; Zhang *et al.*, 1990).

Nearly all of the subjects screened in 1983 had squamous-cell diagnoses, but only 11% of them had columnar-cell diagnoses. The most likely reason for the lower number of columnar-cell diagnoses is that the balloon sampled the upper stomach less well than it sampled the squamous esophagus. Another contributing factor may have been that the cytoplasmic differentiation of cells was not always clear, and the cytologists assumed that cells were squamous unless there was definite evidence of glandular origin. Finally, columnar cells may have been identified but not considered important, and thus not reported when they were a minority of the cells present.

The prevalence of squamous dysplasia (dysplasia 1 and dysplasia 2 together) in the 1983 screening was 26.9%. This was significantly higher than the 1.2% to 6.7% prevalence rates for squamous dysplasia reported in balloon cytology screenings

from Linxian in the 1970s (Coordinating Group, 1975; Shu *et al.*, 1978; Li and Shiang, 1979; Li, 1982; Follow-up Group, 1987; Lu *et al.*, 1988). This increase in the reported prevalence of dysplasia was probably due more to changes in cytologic classification and reporting than to real changes in disease occurrence. Several factors may have contributed to an increase in cases classified cytologically as squamous dysplasia. Most importantly, there was a change in the cytologic criteria for dysplasia 1 and dysplasia 2: in the screenings before 1983, at least 5 cells meeting the criteria for dysplasia 1 or dysplasia 2 had to be found in a patient's smears before he or she was given a cytologic diagnosis of dysplasia (Shen and Shu, 1982; Shen, 1984); beginning in 1983, finding a single dysplastic cell was sufficient to make these diagnoses. Additionally, there was a change in the reason for screening: the purpose of the balloon screenings before 1983 was to identify patients with cancer; in the 1983 examination, however, one of the main purposes was to identify patients with dysplasia for inclusion in the dysplasia trial, so the cytologists were probably more likely to notice and report this morphology. It is also possible that the real prevalence of biologically pre-cancerous esophageal lesions increased in the years before 1983, but a large increase in such lesions appears unlikely, since the esophageal-cancer rates reported from the tumor registry of the Esophageal Cancer Institute in Linxian remained essentially stable during the 1970s and 1980s (Zhang *et al.*, 1990).

The prevalence of squamous-cell cancer in the 1983 screening was 2.1%, which was somewhat higher than the 1.1% to 1.6% prevalence rates reported from previous screenings in Linxian (Coordinating Group, 1975; Shu *et al.*, 1978; Li and Shiang, 1979; Li *et al.*, 1980; Follow-up Group, 1987; Lu *et al.*, 1988). There were no differences in the cytologic criteria for cancer between the 1983 screening and earlier surveys, so this observed change in prevalence may reflect a real change in disease occurrence. As noted above, however, the overall rates of esophageal cancer recorded in Linxian during this period remained stable.

One other difference in cytologic classification between the 1983 examination and earlier screenings should be noted. In 1983, the category near-cancer (jin ai) was used between

dysplasia 2 and cancer. Some earlier screenings had no additional categories between dysplasia and cancer, while others used the category suspicious for cancer (kě yí ái). Near-cancer and suspicious for cancer, however, were not equivalent terms. Near-cancer was a category at the severe end of a morphologic continuum containing dysplasia 1 and dysplasia 2, while suspicious for cancer was used when the cytologist felt that a cancer was probably present but had not been sampled sufficiently to yield completely diagnostic cells.

The diagnostic categories and criteria used in the 1983 screening were used unchanged throughout the Linxian nutrition intervention trials.

The esophageal cytologic categories and criteria used in this screening were developed and have been used almost exclusively in China, and there has not yet been a detailed comparison of these criteria with those most commonly used elsewhere in the world. The predictive value of these criteria has been documented, however, in 2 follow-up studies in Linxian correlating Chinese esophageal cytologic diagnoses from a 1975 mass screening with subsequent development of esophageal cancer. In the first study, 17,898 subjects initially free of cancer were followed up by interviews 9 years after the screening; the cumulative incidence of esophageal cancer in subjects with initial cytologic diagnoses of normal, hyperplasia, and dysplasia were 3.4%, 4.7%, and 10.1% (Follow-up Group, 1987). In the second study, 958 subjects without cancer were

followed by periodic medical examinations and medical record abstracts for 11 years; the relative risks for esophageal-cancer incidence in people with cytologic diagnoses of normal, hyperplasia, and dysplasia were 1.00, 1.02, and 2.39 (2.90 after age-adjustment) (Lu *et al.*, 1988). Follow-up of the individuals in the 1983 screening is in progress.

An understanding of the correlation of Chinese esophageal cytologic diagnoses with endoscopic biopsy diagnoses is also incomplete. The one published study (Muñoz *et al.*, 1982) found little correlation between cytologic and histologic diagnoses in 251 subjects, but the endoscopic examination was performed 5 years after the cytologic examination and sampled only a small fraction of the esophageal mucosa. Additional studies with more closely spaced cytologic and endoscopic examinations and a wider histologic sampling of the esophagus are needed to clarify the true correlation of these 2 diagnostic methods.

In summary, the 1983 balloon cytology screening in Linxian showed high prevalences of squamous-cell and columnar-cell dysplasia and cancer, consistent with the high rates of esophageal cancer in this population. Distinctive gender and age patterns were observed. The prevalence of squamous-cell dysplasia was significantly higher than in earlier balloon cytology screenings in Linxian, probably reflecting changes in cytologic classification.

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